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HLA-C Antigen Mismatch Is Associated with Worse Outcome in Unrelated Donor Peripheral Blood Stem Cell Transplantation

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The association between HLA matching and outcome in unrelated-donor peripheral blood stem cell (PBSC) transplantation has not yet been established. In the present study, a total of 1933 unrelated donor–recipient pairs who underwent PBSC transplantation between 1999 and 2006 for acute myelogenous leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, or chronic myelogenous leukemia and received high-resolution HLA typing for HLA-A, -B, -C, -DRB1, -DQA1, and -DQB1 were included in the analysis. Outcomes were compared between HLA-matched and HLA-mismatched pairs, adjusting for patient and transplant characteristics. Matching for HLA-A, -B, -C, and -DRB1 alleles (8/8 match) was associated with better survival at 1 year compared with 7/8 HLA-matched pairs (56% vs 47%). Using 8/8 HLA–matched patients as the baseline (n = 1243), HLA-C antigen mismatches (n = 189) were statistically significantly associated with lower leukemia-free survival (relative risk [RR], 1.36; 95% confidence interval [CI], 1.13-1.64; $P = .0010$), and increased risk for mortality (RR, 1.41; 95% CI, 1.16-1.70; $P = .0005$), treatment-related mortality (RR, 1.61; 95% CI, 1.25-2.08; $P = .0002$), and grade III-IV graft-versus-host disease (RR, 1.98; 95% CI, 1.50-2.62; $P < .0001$). HLA-B antigen or allele mismatching was associated with an increased risk for acute GVHD grade III-IV. No statistically significant differences in outcome were observed for HLA-C allele (n = 61), HLA-A antigen/allele (n = 136), HLA-DRB1 allele (n = 39), or HLA-DQ antigen/allele (n = 114) mismatches compared with 8/8 HLA–matched pairs. HLA mismatch was not associated with relapse or chronic GVHD. HLA-C antigen–mismatched unrelated PBSC donors were associated with worse outcomes compared with 8/8 HLA–matched donors. The study's limited power due to small sample size precludes conclusions about other mismatches.

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INTRODUCTION

Unrelated donors have provided a vital resource for patients who do not have an HLA-matched relative. Approximately 50% of allogeneic hematopoietic cell transplantations (HCTs) reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) use unrelated donors. Over the past decade, the number of peripheral blood stem cell (PBSC) grafts facilitated by the National Marrow Donor Program (NMDP) has grown substantially, such that currently around 75% of unrelated grafts are PBSC (NMDP

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statistics). In addition, approximately 30% of all PBSC products are mismatched for one or more of the recipient's HLA loci. Previous NMDP/CIBMTR studies evaluating the effects of HLA mismatch included predominantly bone marrow (BM) recipients. Given that the number of unrelated donor PBSC transplantations in the NMDP registry has now reached sufficient quantity for preliminary analysis, the present study was designed to determine the association of HLA mismatch in PBSC transplantation with survival, relapse, graft-versus-host disease (GVHD), and transplantation-related mortality (TRM).

Previous studies from the NMDP/CIBMTR in the setting of BM transplantation have shown an association between HLA mismatch and with worse outcomes [1,2]. In particular, single mismatches at HLA-A, -B, -C, or DRB1 were associated with increased risk for TRM and acute GVHD compared with 8/8 HLA–matched pairs. Isolated HLA-DQ mismatches did not appear to be detrimental. Reports from the Fred Hutchinson Cancer Research Center and the Japanese Marrow Donor Program also support the concept that disparities involving HLA class I alleles are independent risk factors for acute GVHD, TRM, and overall survival [3,4].

In the 1990s, collection of granulocyte-colony stimulating factor (G-CSF)-mobilized PBSCs was introduced as an alternative to BM donation for volunteer unrelated donors [5]. Advantages of PBSCs over BM include more rapid engraftment of neutrophils and platelets for patients and the ability to avoid the operating room for donors and physicians. Retrospective studies have found similar rates of acute GVHD, TRM, relapse, and survival with unrelated donor PBSCs and BM, but an increased incidence of extensive chronic GVHD with PBSCs [6].

Although PBSCs have supplanted BM as the most common source of unrelated hematopoietic stem cells, the impact of HLA mismatch on outcomes after unrelated PBSC transplantation has not yet been well studied. The present study was undertaken to compare the outcomes of HLA-mismatched compared with HLA-matched unrelated donor transplantation using PBSCs as the graft source. Identification of mismatched HLA loci associated with particularly poor outcomes may help guide donor selection when an 8/8 HLA–matched donor is not available and allogeneic transplantation is recommended.

PATIENTS AND METHODS

Study Population

The study population included all patients reported to the NMDP/CIBMTR registries who received an unrelated PBSC transplant between 1999 and 2006 for acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), or chronic myelogenous leukemia (CML) for whom retrospective high-resolution HLA typing results were available for both patient and unrelated donor. Diseases were categorized as early phase (acute leukemia in first complete remission [CR1], CML in first chronic phase, and MDS-refractory anemia [RA]), intermediate phase (acute leukemia in second remission [CR2] and CML in accelerated or second chronic phase), or advanced phase (acute leukemia advanced beyond CR2 or not in remission, CML in blast crisis, MDS-RA with excess blasts [RAEB] or in transformation [RAEB-T]). Conditioning regimens were defined as "myeloablative" if the patient received total body irradiation (TBI) at a dose >500 cGy if given as a single dose or >800 cGy if given in fractions, received busulfan at a dose ≥ 9.5 mg/kg, or received melphalan at a dose >150 mg/m^2. All other regimens were considered either reduced-intensity conditioning (RIC) or nonmyeloablative (NM) conditioning [7]. All patients received T cell–replete grafts.

All patients included in this study signed informed consent for reporting of clinical information to the NMDP/CIBMTR registries in accordance with the Declaration of Helsinki. Twenty-seven (1.3%) of otherwise eligible patients were excluded to account for lack of consent to use the data of surviving patients or to adjust for potential bias by excluding appropriately the same percentage of deceased patients using a biased coin randomization, with exclusion probabilities based on characteristics associated with not providing consent for use of the data in survivors.

HLA Typing

High-resolution typing for HLA-A, -B, -C, -DRB1, -DQA1, -DQB1, -DPA1, and -DPB1 was performed as described previously [1]. Low-resolution (serologic or antigen level) disparities involved conversion of the DNA-based typing to its lower-level serologic equivalent, usually by collapsing the 4-digit typing result back to its first 2 digits, with the exception of a few HLA-B alleles that were mapped to their corresponding serologic specificities. Antigen and allele mismatches at HLA-DRB1 were combined. Mismatches at HLA-DQ were scored if there was disparity for either the -DQA1 or the -DQB1 sequence, because both -DQA1 and -DQB1 genes contribute to the expression of a single heterodimeric HLA-DQ protein. HLA-DQA1 was not considered for determination of antigen matching. Directional mismatches (graft-vs-host or host-vs-graft) were considered appropriate in the analysis of GVHD and engraftment, as described previously [8]. Mismatches at homozygous alleles were considered single mismatches.

Biostatistical Methods

Probabilities for mortality and leukemia-free survival (LFS) were calculated using the Kaplan-Meier estimator, and survival curves were compared using the log-rank

test. All other outcomes were estimated using the cumulative incidence function [9]. Death was considered a competing risk for all of the endpoints except mortality and LFS. Relapse also was considered a competing event for TRM. Patients were censored if they underwent a second HCT or were alive at last follow-up.

The association between number and type of HLA mismatches was evaluated using separate multivariate proportional hazards models, adjusting for significant clinical covariates. Similar to the 2007 NMDP/CIBMTR survey [2], this approach compares subgroups of HLA-mismatched pairs with 8/8-matched pairs. A P value <.01 was considered statistically significant because of multiple testing.

All models were tested for significant clinical covariates including disease, disease stage, Karnofsky performance score (KPS), or Lansky performance score, patient race, patient age, GVHD prophylaxis, conditioning regimen, donor age, donor–patient cytomegalovirus (CMV) serology, T cell depletion, use of TBI, patient–donor sex match, and year of transplantation. Models were adjusted for any clinical factors that were related to a given outcome at $P < .05$. All variables were tested for affirmation of the proportional hazards assumption and for interactions with HLA matching. No significant interactions were identified.

RESULTS

Patient and Transplant Characteristics

Characteristics of the study population are shown in Table 1. The median follow-up duration was 2 years (range, 0.3-7.4 years).

HLA-DQ and -DP Mismatch

HLA-DQ mismatch was not statistically associated with survival in patients otherwise matched for HLA-A, -B, -C, and -DRB1. The relative risk (RR) for mortality for single -DQ allele (n = 68) or antigen (n = 46) mismatch was 0.97 (95% confidence interval [CI], 0.71-1.34; $P = .87$) and 1.35 (95% CI, 0.95-1.96; $P = .10$), respectively, compared with a full match (n = 1125). Because there were no statistically significant differences in LFS, relapse, TRM, and acute and chronic GVHD, HLA-DQ mismatching was not considered further in the determination of HLA-matching status. Information on HLA-DP matching was available in only 20% of donor–recipient pairs, too few to be sufficient for analysis; accordingly, HLA-DP mismatch was not considered in the subsequent analyses.

Number and Type of HLA Mismatches

Table 2 shows the association between 1 or 2 allele and/or antigen mismatches and the transplantation outcomes evaluated. HLA-mismatched pairs that contained at least 1 antigen mismatch had statistically worse survival and disease-free survival than pairs who were 8/8 matched; however, survival of 7/8 allele mismatches was not statistically different than 8/8 matched pairs. Among 6/8-matched pairs, 29 pairs with double-allele mismatches did not have worse survival than 8/8-matched pairs (RR, 1.21; 95% CI, 0.77-1.90; $P = .42$), but the small number of patients limited the power of this analysis. The 6/8-matched pairs that had at least 1 antigen mismatch had statistically worse survival than the 8/8-matched pairs.

For TRM, any degree of HLA mismatch was associated with worse outcome. In contrast, HLA mismatch was not associated with a lower risk of relapse. Grade III-IV acute GVHD was increased with any degree of HLA mismatch (Table 2). There was no association between number and type of HLA mismatches and grade II-IV acute GVHD or chronic GVHD.

Locus-Specific HLA Mismatch

Table 3 presents the results of locus-specific analysis of single mismatched pairs for the outcomes of interest. Note that the power of this analysis is limited for some subgroups because of small sample sizes. Thus, although evidence of a statistically significant worse outcome can be accepted, the absence of such a finding does not mean that a mismatch is "safe." Mismatch of a single HLA-C antigen was associated with a statistically significantly higher risk for mortality, TRM, and grade III-IV acute GVHD and lower LFS. At 2 years, unadjusted

Table 1. Characteristics of 1933 Unrelated Donor PBSC Transplant Recipients

Variable	Number (%)
Age, years, median (range)	46 (<1-74)
Age group, n (%)	
0-9 years	55 (3%)
10-19 years	119 (6%)
20-29 years	251 (13%)
30-39 years	276 (14%)
40-49 years	421 (22%)
50 and older	811 (42%)
Males, n (%)	1078 (56%)
KPS/Lansky Performance Score ≥90, n (%)	1163 (66%)
Disease, n (%)	
AML	946 (49%)
ALL	359 (19%)
CML	218 (11%)
MDS	410 (21%)
Disease stage, n (%)	
Early	682 (35%)
Intermediate	453 (24%)
Advanced (late)	798 (41%)
Conditioning regimen, n (%)	
Myeloablative	1260 (65%)
RIC/NM	673 (35%)
Year of HCT, n (%)	
1999-2002	395 (20%)
2003-2006	1538 (80%)
Median follow-up of survivors, months, median (range)	24 (3-89)

survival was 32% for HLA-C mismatches, compared with 44% for 8/8 matches ($P = .003$); LFS was 26% compared with 40% ($P = .0002$); and cumulative incidence of TRM was 40% compared with 28% ($P = .002$). Mismatch at a single HLA-B allele or antigen was also associated with increased risk of grade III-IV acute GVHD. The risks of relapse and chronic GVHD were not statistically different for 8/8 matches compared with any locus-specific mismatch, including HLA-C antigen–mismatched pairs.

Myeloablative versus Nonmyeloablative Conditioning

Table 4 compares HLA-C antigen–mismatched pairs, other 7/8 antigen (non-C)– mismatched pairs, 7/8 allele–mismatched pairs, and 8/8-matched pairs by conditioning regimen intensity. HLA-C antigen mismatch is associated with an increased risk of mortality compared with 8/8 matches for patients given either myeloablative conditioning (n = 122; RR, 1.40; 95% CI, 1.10-1.78; $P = .006$) or nonmyeloablative conditioning or RIC (n = 65; RR, 1.40; 95% CI, 1.01-1.95; $P = .04$). In contrast, other 7/8 (non-C) antigen–mismatched pairs and 7/8 allele–mismatched pairs did not have statistically higher mortality compared with 8/8-matched pairs in either the myeloablative or nonmyeloablative/RIC group.

Mismatched PBSC Compared with Mismatched Marrow

To gain insight into whether using BM instead of PBSC would be advantageous when the use of an HLA-mismatched donor is planned, we compared the PBSC recipients in our research dataset with the recipients of BM grafts in the analysis reported by Lee et al. [2]. No statistically significant differences in mortality were seen when HLA-mismatched transplantations were performed with PBSC or with BM. The risk for mortality at 1 year did not differ between recipients of 7/8 antigen–mismatched BM grafts (n = 547) and recipients of 7/8 antigen–mismatched PBSC grafts (n = 293) (RR, 1.13; 95% CI, 0.93-1.40; $P = .26$), or between the subgroups of BM (n = 321) and PBSC (n = 187) recipients when the mismatch involved a single HLA-C antigen (RR, 1.08; 95% CI, 0.84-1.70; $P = .55$). These results, which are adjusted for disease, disease status, and KPS pretransplantation, suggest there is no advantage to changing the graft source from PBSC to BM when using a HLA-mismatched donor even if the antigen mismatch is at HLA-C. Year of transplantation

Table 2. Effect of the Number of Mismatched HLA Antigens or Alleles on Mortality and Relapse among Recipients of Unrelated PBSC Transplants, Adjusted for Patient and Transplant Characteristics

	n	RR	95% CI	P
Mortality				
8/8 match	1243	1.00		
One allele mismatch	208	1.11	0.91-1.35	.30
One antigen mismatch	293	1.32	1.12-1.55	.0007
Two allele/antigen mismatch	99	2.32	1.78-3.02	<.0001
TRM				
8/8 match	1243	1.00		
One allele mismatch	208	1.41	1.09-1.81	.008
One antigen mismatch	293	1.54	1.24-1.91	.0001
Two allele/antigen mismatch	99	3.16	2.28-4.37	<.0001
LFS				
8/8 match	1243	1.00		
One allele mismatch	208	1.15	0.95-1.38	.15
One antigen mismatch	293	1.29	1.10-1.51	.0013
Two allele/antigen mismatch	99	2.25	1.74-2.92	<.0001
Relapse				
8/8 match	1243	1.00		
One allele mismatch	208	0.90	0.68-1.20	.48
One antigen mismatch	293	1.04	0.82-1.32	.76
Two allele/antigen mismatch	99	1.24	0.78-1.98	.36
Acute GVHD II-IV				
8/8 match	1243	1.00		
One allele mismatch	208	0.93	0.93-1.37	.24
One antigen mismatch	266	1.21	1.02-1.43	.03
Two allele/antigen mismatch	97	1.18	0.85-1.64	.31
Acute GVHD III-IV				
8/8 match	1243	1.00		
One allele mismatch	208	1.59	1.20-2.09	.0012
One antigen mismatch	266	1.93	1.53-2.44	<.0001
Two allele/antigen mismatch	97	2.43	1.64-3.59	<.0001
Chronic GVHD				
8/8 match	1243	1.00		
One allele mismatch	208	1.00	0.81-1.23	.97
One antigen mismatch	266	1.15	0.95-1.40	.14
Two allele/antigen mismatch	97	1.03	0.69-1.54	.88

Table 3. Effect of the Locus of Mismatched HLA Antigens or Alleles on Mortality, Relapse, and GVHD among Recipients of Unrelated PBSC Transplants, Adjusted for Patient and Transplant Characteristics

	n	RR	95% CI	*P*
Mortality				
8/8 match	1243	1.00		
HLA-A allele mismatch	51	1.16	0.80-1.67	.43
HLA-A antigen mismatch	85	1.17	0.88-1.55	.29
HLA-A allele or antigen mismatch*	136	1.17	0.93-1.47	.19
HLA-B allele mismatch	57	1.29	0.92-1.82	.14
HLA-B antigen mismatch	16	1.01	0.50-2.04	.97
HLA-B allele or antigen mismatch*	73	1.22	0.90-1.67	.19
HLA-C allele mismatch	61	0.82	0.57-1.19	.30
HLA-C antigen mismatch	189	1.41	1.16-1.70	.0005
HLA-DRB1 mismatch	39	1.30	0.87-1.94	.20
TRM				
8/8 match	1243	1.00		
HLA-A allele mismatch	51	1.47	0.92-2.35	.11
HLA-A antigen mismatch	85	1.33	0.91-1.93	.14
HLA-A allele or antigen mismatch*	136	1.37	1.01-1.86	.04
HLA-B allele mismatch	57	1.75	1.14-2.69	.01
HLA-B antigen mismatch	16	1.65	0.81-3.38	.17
HLA-B allele or antigen mismatch*	73	1.74	1.20-2.51	.004
HLA-C allele mismatch	61	1.02	0.62-1.67	.93
HLA-C antigen mismatch	189	1.61	1.25-2.08	.0002
HLA-DRB1 mismatch	39	1.53	0.94-2.51	.09
LFS				
8/8 match	1243	1.00		
HLA-A allele mismatch	51	1.20	0.84-1.71	.31
HLA-A antigen mismatch	85	1.11	0.84-1.48	.46
HLA-A allele or antigen mismatch*	136	1.15	0.91-1.44	.24
HLA-B allele mismatch	57	1.28	0.93-1.77	.13
HLA-B antigen mismatch	16	1.20	0.64-2.26	.57
HLA-B allele or antigen mismatch*	73	1.27	0.95-1.69	.12
HLA-C allele mismatch	61	0.92	0.65-1.30	.62
HLA-C antigen mismatch	189	1.36	1.13-1.64	.001
HLA-DRB1 mismatch	39	1.27	0.86-1.87	.22
Relapse				
8/8 match	1243	1.00		
HLA-A allele mismatch	51	0.91	0.53-1.56	.73
HLA-A antigen mismatch	85	0.97	0.62-1.52	.90
HLA-A allele or antigen mismatch*	136	0.95	0.67-1.36	.79
HLA-B allele mismatch	57	1.03	0.62-1.71	.91
HLA-B antigen mismatch	16	0.42	0.10-1.74	.23
HLA-B allele or antigen mismatch*	73	0.89	0.55-1.44	.64
HLA-C allele mismatch	61	0.80	0.48-1.32	.38
HLA-C antigen mismatch	189	1.09	0.83-1.44	.53
HLA-DRB1 mismatch	39	0.91	0.48-1.72	.77
GVHD grade II-IV				
8/8 match	1279	1.00		
HLA-A allele mismatch	54	0.99	0.67-1.44	.93
HLA-A antigen mismatch	79	1.33	1.00-1.77	.05
HLA-A allele or antigen mismatch*	136	1.18	0.94-1.50	.16
HLA-B allele mismatch	56	0.99	0.69-1.44	.97
HLA-B antigen mismatch	16	1.51	0.85-2.69	.16
HLA-B allele or antigen mismatch*	73	1.11	0.81-1.52	.52
HLA-C allele mismatch	64	1.16	0.83-1.62	.40
HLA-C antigen mismatch	168	1.12	0.90-1.39	.30
HLA-DRB1 mismatch	34	1.60	1.06-1.80	.03
GVHD grade III-IV				
8/8 match	1279	1.00		
HLA-A allele mismatch	54	1.38	0.81-2.37	.24
HLA-A antigen mismatch	79	1.54	1.01-2.34	.04
HLA-A allele or antigen mismatch*	136	1.46	1.04-2.06	.03
HLA-B allele mismatch	56	1.91	1.21-3.02	.006
HLA-B antigen mismatch	16	3.25	1.66-6.36	.0006
HLA-B allele or antigen mismatch*	73	2.22	1.51-3.25	<.0001
HLA-C allele mismatch	64	1.17	0.69-1.97	.56
HLA-C antigen mismatch	168	1.98	1.50-2.62	<.0001
HLA-DRB1 mismatch	34	1.87	1.05-3.35	.03
Chronic GVHD				
8/8 match	1279	1.00		
HLA-A allele mismatch	54	0.99	0.68-1.45	.97

(*Continued*)

Table 3. (*Continued*)

	n	RR	95% CI	*P*
HLA-A antigen mismatch	79	1.24	0.90-1.69	.19
HLA-A allele or antigen mismatch*	136	1.12	0.87-1.43	.38
HLA-B allele mismatch	56	0.87	0.56-1.36	.55
HLA-B antigen mismatch	16	1.14	0.59-2.22	.69
HLA-B allele or antigen mismatch*	73	0.94	0.64-1.36	.73
HLA-C allele mismatch	64	1.03	0.73-1.45	.86
HLA-C antigen mismatch	168	1.12	0.88-1.42	.35
HLA-DRB1 mismatch	34	1.11	0.68-1.84	.67

*From a separate model in which allele and antigen mismatches were combined for the A and B loci.

and intensity of the conditioning regimen were not found to be statistically significant in these models.

DISCUSSION

This study of HLA matching and outcomes of unrelated-donor PBSC transplantation shows that HLA mismatching in general, and HLA-C antigen and HLA-B allele and antigen mismatching in particular, are associated with statistically worse outcomes compared with 8/8 HLA matching. No statistically significant associations between HLA mismatching and relapse or chronic GVHD were observed. Mismatching at HLA-DQ was not associated with statistically significantly worse outcomes and thus was disregarded when determining HLA matching. Overall, our findings are similar to those from previous studies of the effects of HLA mismatching in BM transplantation in largely Caucasian cohorts [1,2].

Most of the patients included in the previously reported sequential retrospective studies of high-resolution HLA matching received BM grafts. Compared with BM, PBSCs contain 10-fold more $CD3^+$ cells and 4-fold more $CD34^+$ cells on average [10]. The relative contribution of cell subsets also differ; for example, PBSCs have a ~3-fold higher CD3:CD 34 ratio and a ~25-fold higher CD14:CD34 ratio than BM, as well as a greater proportion of CD4 cells with an anti-inflammatory (Th2) phenotype [11-14]. Other studies have indicated relatively more DC2 dendritic cells and skewing of the DC1:DC2 ratio to DC2 cells within PBSCs [14]. All PBSC donors receive G-CSF, whereas most unrelated BM donors do not. The differences in cellular characteristics of the two products suggest, at a minimum, that the effect of HLA mismatching shown for BM transplants cannot be assumed to be applicable to PBSC products.

Although our results do not define an "optimal" mismatch for a PBSC transplant, they clearly show that an HLA-C antigen mismatch is associated with lower survival and higher TRM in both the single- and double-mismatch settings. This conclusion is consistent with findings of Flomenburg et al. [1] and Lee et al. [2]. In the study of Lee et al. [2], HLA-C antigen mismatch (RR, 1.22; 95% CI 1.06-1.39; $P = .004$), HLA-A antigen mismatch (RR, 1.24; 95% CI, 1.02-1.52; $P < .001$), and HLA-DRB1 allele mismatch (RR, 1.42; 95% CI, 1.13-1.80; $P = .003$) were associated with worse survival compared with the 8/8 match. Our study of PBSC transplantation also found a statistically significant relationship between HLA-B mismatch and increased risk for grade III-IV acute GVHD, but no association with survival. It is notable that the higher rates of severe acute GVHD observed in HLA-C antigen and HLA-B antigen and allele–mismatched pairs did not translate into higher chronic GVHD rates or lower relapse rates. We hypothesize that this could possibly be due to the higher TRM generally associated with grade III-IV acute GVHD, the fact that chronic GVHD is more closely linked with prevention of relapse, or our small sample size, which limited the study's power.

The main limitation of the present study is the small number of observations in some of the subgroups, which might have led to erroneous estimation of the effect of a specific HLA mismatch and limited power in comparisons. In addition, the median follow-up period of 2 years is relatively short compared with that in previous studies of HLA matching in BM

Table 4. Association of 7/8 HLA-C Antigen Mismatch with Mortality in Patients Conditioned with a Myeloablative or an RIC/NM Regimen

	Myeloablative				RIC/NM			
	n	RR*	95% CI	*P*	n	RR*	95% CI	*P*
8/8	796	1.00			447	1.00		
7/8 HLA-C antigen	122	1.40	1.10-1.78	.006	65	1.40	1.01-1.95	.04
7/8 other antigen	80	1.23	0.91-1.66	.18	26	0.93	0.54-1.61	.80
7/8 allele	130	1.14	0.88-1.47	.32	78	.82	0.82-1.55	.45

*Adjusted for disease and KPS; stratified by disease status and GVHD prophylaxis.

transplantation. NM/RIC transplantations composed 35% of our study population, but represent approximately 50% of the procedures currently performed. As the number of PBSC transplants increases and follow-up lengthens, a subsequent analysis will be important to update our observations and to consider other factors that could possibly affect outcomes, such as killer Ig-like receptor (KIR) status [15-19] or HLA-DP matching [19,20]. For example, in the BM setting, the earlier study of Flomenberg et al. [1] (n = 1874) did not find an increased risk associated with single allele mismatches [1], whereas the larger Lee et al. study (n = 3857) found an association between a single allele or antigen mismatch and adverse outcomes [2].

Neither of these previous BM studies included substantial numbers of NM or RIC transplants, which typically use PBSC grafts. A reasonable concern with these conditioning regimens is that rejection of a mismatched graft or risk for relapse may be amplified because host T or natural killer (NK) cells might survive less-intensive conditioning. Our analysis showed that HLA-C antigen mismatch is associated with higher risk for overall mortality and TRM, but not relapse, after NM/RIC PBSC HCT, similar to that for myeloablative HCT (relapse data not shown). Unfortunately, we lack data on KIR genotyping to allow a refined analysis of possible NK cell effects.

In cases when HLA-C antigen mismatching cannot be avoided, one might wonder whether a BM graft might be better tolerated than a PBSC graft. Our exploratory analysis found no advantage to using BM as the cell source from a donor with an isolated HLA-C antigen mismatch. We caution that the present retrospective analysis cannot take into consideration all factors that might introduce bias. Our presentation of these results is intended not to address the question of whether one graft source is preferable over the other, but rather to provide the best available data pending larger studies. In an analysis by Eapen et al. [21], outcomes of 7/8-matched BM and 7/8-matched PBSC transplantations appeared to be similar, although direct comparisons were not performed and locus-specific data were not provided. In October 2009, the Blood and Marrow Transplant Clinical Trials Network finished enrollment of a 550-patient prospective multicenter randomized trial to assess the risks and benefits of BM versus PBSCs from unrelated donors. A planned subgroup analysis of HLA-mismatched grafts has been included in the study design, the results of which will be important for addressing the issues raised in our analysis.

It is important to remember that our results are not meant to imply that an HLA-mismatched graft should not be used, only that the greater risks compared with 8/8 HLA–matched grafts should be recognized when present. For many patients, the best hope for long-term LFS will remain allogeneic HCT, even with a less-than-optimal donor.

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